

# Postnatal circulatory adaptation in healthy term and preterm neonates

N J Evans, L N J Archer

## Abstract

Thirty seven healthy infants (18 born at full term and 19 preterm) were studied serially with cross sectional and Doppler echocardiography to compare their postnatal circulatory adaptation. Pulmonary artery pressure was assessed by its inverse relationship with the ratio of pulmonary artery time to peak velocity and right ventricular ejection time measured from Doppler waveform. Patency of the ductus arteriosus and interatrial shunting were assessed by imaging and Doppler ultrasound. The ratio rose after birth in all infants; it rose more slowly in the preterm infants. After 6 hours of age the mean was significantly less in the preterm group, the greatest difference being between 25 and 36 hours. By 73 to 96 hours the difference was no longer significant. There was a trend towards later ductal closure in the preterm infants but this was not significant. Atrial shunting level varied, but some left to right shunting was seen in all infants satisfactorily studied. Pulmonary artery pressure seems to fall more slowly after preterm birth even in the absence of respiratory problems, but ductal shunting persisting for more than three days is unusual in healthy preterm infants.

Two dimensional and Doppler echocardiography provide a non-invasive method for studying the circulatory adaptation to extra-uterine life in humans. The ductus arteriosus and foramen ovale can be seen, and analysis of Doppler wave forms has lead to the development of indirect methods for assessing pulmonary artery pressure. The ratio of pulmonary artery time to peak velocity (TPV) and right ventricular ejection time (RVET) as measured from the Doppler waveform has a close inverse correlation with mean pulmonary artery pressure. This correlation has been validated against direct catheter pressure measurement in children and adults,<sup>1-3</sup> and is a good way of studying pulmonary haemodynamics in the newborn. Ultrasound studies of the transitional circulation in infants born at full term have shown that the TPV:RVET ratio rises significantly over the first 24 to 36 hours of life with ductal closure invariably complete by 48 hours.<sup>4-6</sup> Postnatal catheter studies using direct pressure measurements have shown a similar rate of fall both in pulmonary artery pressure and in time taken for complete ductal closure.<sup>7</sup> No such measurements have been published for healthy preterm infants. Such data is important for comparative purposes, as one of the

potential uses of the TPV:RVET ratio is to study pulmonary artery pressure in infants with respiratory problems. In this study, using two dimensional and Doppler echocardiography, the rate of circulatory adaptation to extrauterine life was compared between healthy infants born at full term and those born prematurely.

## Patients and methods

All subjects were studied with an ATL Ultramark 4 scanner and range gated pulsed Doppler. Cross sectional imaging was done with a 7.5 MHz transducer incorporating a 5 MHz pulsed Doppler crystal.

The procedure for each study was as follows: the pulmonary artery was visualised from the parasternal long axis view. The Doppler sample volume was placed just distal to the pulmonary valve and the pulmonary artery flow pattern was recorded. The pattern was frozen on the screen and the time intervals were measured using the incorporated Doppler measurement calipers; a print was then taken. TPV was measured as the time interval between the systolic Doppler waveform leaving the baseline and reaching its peak velocity. RVET was the time interval between the systolic waveform leaving and returning to the baseline. A mean of three systolic waveforms was taken. A second observer, who was unaware of the initial results, repeated the measurements on 50 of the Doppler prints using a computer digitiser system. The correlation coefficient between the 'on line' and repeat measurements was 0.92.

The ductus arteriosus was then visualised from the high left parasternal 'ductal' view.<sup>8</sup> The Doppler sample volume was placed in the pulmonary end of the duct and the flow pattern recorded. The duct was designated closed when it could not be seen, and no flow could be detected on a pulsed Doppler search of the pulmonary end of the duct. Finally the foramen ovale was visualised from the subcostal four chamber view, and when possible the flow pattern was recorded.

The infants were initially studied in the first 12 hours after birth; studies were then repeated at 24 hour intervals until a steady state was reached.

Statistical analysis was by the unpaired Student's *t* test and the  $\chi^2$  test; *p* values of <0.05 were accepted as significant.

Thirty seven infants were studied, 18 born at full term and 19 preterm (table 1). All the preterm infants had either minimal or no extra oxygen requirements; two were initially placed in low concentrations of oxygen (<30%) but

Neonatal Unit,  
Department of  
Paediatrics,  
John Radcliffe  
Maternity Hospital,  
Oxford

N J Evans  
L N J Archer

Correspondence to:  
Dr N J Evans,  
Department of  
Paediatrics, John Radcliffe  
Hospital, Headington,  
Oxford OX3 9DU.

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Table 1 Comparability of the groups. Figures are given as mean (range)

	Infants born at full term (n=18)	Preterm infants (n=19)
Gestational age (weeks)	39.8 (38–42)	31.8 (28–34)*
Birth weight (g)	3300 (2650–4030)	1610 (950–2050)

\*Seven were between 28 and 31 weeks' gestation.

both were breathing air within 24 hours. Consent to the study was obtained from all the mothers, and it was approved by the central Oxford research ethics committee.

### Results

The TPV:RVET ratio rose in all infants in the early postnatal period. To compare the rate of change between those born at full term and those who were preterm the measurements were divided into postnatal age groups (table 2). For each age group the mean (SD) TPV:RVET ratio was plotted at the mean measurement time (figure). In the infants born at full term the TPV:RVET ratio rose rapidly over the first 30 hours of life, with only a minimal change after that. The rise in the TPV:RVET ratio was slower in the preterm infants, with the rise levelling out after about 60 hours. Within the first 6 hours, the mean TPV:RVET ratio was 0.23 (0.035) in the infants born at full term and 0.195 (0.042) in the preterm infants; the difference is not significant. In subsequent postnatal age groupings the ratio was significantly less in the preterm infants. Between 25 and 36 hours, the mean TPV:RVET ratio was 0.36 (0.037) in the infants born at full term and 0.29 (0.046) in the preterm infants,  $p < 0.001$ . Between 73 and 96 hours there was no longer any significant difference, the mean being 0.38

Table 2 Total number of studies in each age group

Age group (hours)	Infants born at full term (n=18)	Preterm infants (n=19)
0–6	8	10
7–14	9	8
15–24	0	6
25–36	18	13
37–48	2	6
49–72	17	18
73–96	10	13

Table 3 No (%) of studies in each age group that showed a closed ductus arteriosus. No infant had more than one study in each group. None of the differences are significant

Age group (hours)	Infants born at full term (n=18)	Preterm infants (n=19)
0–19	1/18 (5)	0/17
20–39	12/17 (71)	10/19 (53)
40–59	14/15 (93)	15/17 (88)
≥60	12/12 (100)	18/19 (95)

(0.023) in those born at full term and 0.35 (0.045) in the preterm infants.

During the first 20 hours of life, the duct was closed in one of 18 studies in the infants born at full term and in none of 17 studies in preterm infants (table 3). Between 20 and 39 hours, 12 of 17 studies in infants born at full term and 10 of 19 studies in the preterm infants showed closed ducts; this difference is not significant. After this time most of the ducts were closed in both groups. The latest studies that showed a patent ductus were at 40 hours in an infant born at full term and at 72 hours in a preterm infant.

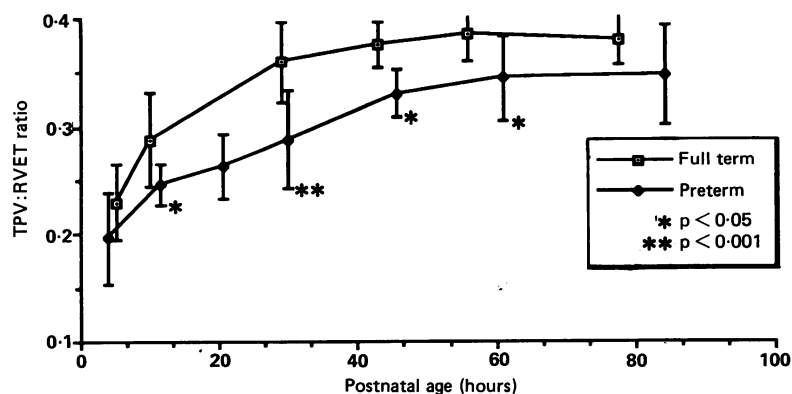
Apart from some of the studies during the first eight hours, the patterns of ductal flow were constant left to right throughout the cardiac cycle. Within the first eight hours, five of 10 studies in infants born at full term and five of nine studies in preterm infants showed bidirectional ductal flow. In these studies the flow was right to left in early right ventricular systole and left to right in late systole and diastole.

The Doppler pattern of flow through the foramen ovale was recorded in all the infants born at full term but, because of incompleteness of the early studies, in only seven of the preterm infants. The pattern of flow was predominantly left to right in all studies, flow was minimal or slightly right to left during ventricular diastole, and then became left to right increasing to a peak during atrial filling in ventricular systole. The velocity of this peak was usually less than 0.4 m/sec but in four of the infants born at full term peak velocities of up to 0.6 m/sec were seen.

### Discussion

We found, using an indirect method of assessment, that pulmonary artery pressure in infants born at full term falls rapidly over the first 30

Comparison of the change in the time to peak velocity: right ventricular ejection time (TPV:RVET) ratio in the main pulmonary artery with postnatal age in healthy infants. For each age group values are shown as mean (SD).



hours of life. This is consistent with previous studies, both those using Doppler assessment<sup>4-6</sup> and those using direct measurement.<sup>7</sup> Emmanouilides *et al*, using catheters, showed a fall in pulmonary artery pressure from a mean of 40 mm Hg within the first 6 hours of life to a mean of 29 mm Hg between 24 and 36 hours.<sup>7</sup> This corresponds to the rise in the TPV:RVET ratio from 0.23 to 0.36 that we found. Our findings suggest, however, that the postnatal fall in pulmonary pressure is slower after preterm birth, even if there are no respiratory problems.

The development of pulmonary vasculature in later gestation has been well studied in fetal animals. Fetal lambs show a steady increase in pulmonary blood flow with a gradual fall in pulmonary vascular resistance during the second half of gestation.<sup>9</sup> Some of this change will be the result of the increase in cross sectional area of the vasculature of the developing fetal lung.<sup>10</sup> Prostaglandins seem to be important factors in the control and maintenance of in utero pulmonary vascular resistance and its subsequent postnatal fall. Prostaglandin synthesis in animal fetal lungs changes with advancing gestation; a predominance of constrictor prostaglandins (prostaglandin  $F_{\alpha_2}$ ) in early gestation gives way to one of dilator prostaglandins (prostaglandin  $I_2$ , prostaglandin  $E_2$ ) nearer full term.<sup>10</sup> After birth, high concentrations of prostaglandin  $I_2$  are found in animal pulmonary veins suggesting that it may act as a mediator of the postnatal fall in pulmonary vascular resistance.<sup>11</sup> A combination of structural and hormonal immaturity may combine to produce a delayed fall in pulmonary artery pressure after preterm birth.

The pattern of flow through the ductus arteriosus was bidirectional in some of the early studies in both groups of infants. This pattern of shunting is seen when pulmonary artery pressure is equal to or slightly less than aortic pressure and thus is compatible with high early postnatal pulmonary artery pressures.<sup>12</sup> In the later studies, as pressures were falling, the pattern of flow was left to right throughout the cardiac cycle. Persistent ductal shunting is a well recognised problem for preterm infants with respiratory distress. Less ductal muscle mass,<sup>13</sup> decreased responsiveness to oxygen induced vasoconstriction,<sup>14</sup> and increased concentrations of dilator prostaglandin<sup>15</sup> have all been implicated in prolonged ductal patency. In preterm infants with no respiratory problems the ductus arteriosus closes within the first 3 to 4 days of life.<sup>16</sup> Our study, which included a larger number of less mature infants, confirms this finding. The latest study time showing a patent duct was 72 hours after birth in an infant of 31 weeks' gestation. Though preterm infants tended to close their ducts later, within the range of gestation that we studied prematurity without respiratory problems did not seem to prolong ductal shunting significantly.

The dominant direction of interatrial shunting was from left to right even in the early postnatal period, which is in keeping with the direct catheter studies that showed that pulmonary diastolic pressures fall earlier than

systolic.<sup>7</sup> The foramen ovale does not completely seal for some time after birth, and our data suggest a degree of incompetence in most infants during the early postnatal period. The degree of that incompetence varies considerably among individual infants, four of the infants born at full term having appreciable atrial shunts. Using cross sectional echocardiography, Fukazawa *et al* found 24 out of 102 normal term infants had visible defects in the atrial septum, which had spontaneously closed in all but one of the infants by 1 year.<sup>17</sup> Thus it seems that the natural history of incompetence of the foramen ovale is for spontaneous closure.

Our results suggest that there are small but significant differences in the speed with which healthy preterm and term infants adapt to life outside the uterus. Though these differences are of physiological rather than clinical importance they do provide normal values from which we can go on to study preterm infants with respiratory disease as well as mature infants with persistent pulmonary hypertension.

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